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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,309	02/21/2002	Michael Brandt	20859	3846

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PATENT LAW DEPARTMENT
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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/081,309	**Applicant(s)** BRANDT ET AL.	
	Examiner Gyan Chandra	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 January 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *06 March 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,4-6,8 and 12-15*.
   Claim(s) withdrawn from consideration: *3,7 and 9-11*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). 1/5/2006
13. ☐ Other: _____.

Continuation of 11 does not place the application in condition for allowance because:

Claims 1-15 are pending. Claims 3, 7, and 9-11 are withdrawn.
Claims 1-2, 4-6, 8, and 12-15 are under examination.
The Information Disclosure Statement (IDS) filed on 1/5/06 replacing a blank sheet due to scanning error has been considered.

Applicant's Response to Final Rejection filed on 9/02/2005 is acknowledged. The rejection of claims 1-2, 4-6, 8, and 12-13 under 35 USC 103 (a), is maintained for the reasons of record in the previous office action mailed on 9/02/2005.
The claimed invention is drawn to a conjugate consisting of a NK4 molecule and a polyethylene glycol group having a molecular weight of about 20-40 kDa wherein polyethylene glycol group has: (i) the formula–CO-(CH2)X-(OCH2CH2)mOR, (ii) is monomethoxy polyethylene glycol and (iii) forms amide group with the amino groups of N-terminal NK4 fragment.

Applicant argues that Nimiki only teaches only modifying HGF via "monoethoxy linear PEG" and would not be applicable to other proteins, in particular if they comprise amino acids other than serine and threonine. Gaetner et al. Teach PEGylation of N-terminus amino acid through Oxime bond formation. Applicant points to Mehvar (2000) and Reddy (2000) references that the PEGylation of IL-8 and G-CSF causes impaired activity and that each protein requires different optimization chemistry.

Applicant's response have been fully considered but it is insufficient to overcome the rejection of claims 1-2, 4-6, 8, and 12-13 under 35 USC 103 (a), as set forth in the last Office action and further because the skill in the art of PEGylation of proteins at N-terminus of a protein is high. For example, Lu and Felix (see abstract: Int J Pept Protein Res 43: 127-138, 1994), Gonzalez et al. (US Patent No. 6, 133,426) teach PEGylation of protein and peptides at the N-terminus by the formation of a covalent bond with -NH2 of the N-terminus amino acid. It is also known in the art that some proteins may be subopitmally active when PEGylation is achieved at the N-terminus and therefore, site specific PEGylation is well practiced. Date et al disclose that within HGF is a four-kringle-containing (NK4) growth factors and the importance of NK4 in growth and invasiveness of carcinoma cells. Namiki et al teach that the modification of HGF by attaching monoethoxy linear and branched PEG(s) at the N-terminus amino acids improves the clearance and in vivo pharmacokinetics of HGF (page 2, line 49-57), as set forth in the previous Office Action. It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to attach PEG molecules to the N-terminus amino acid of NK4 in order to increase clearance, improve in vivo pharmacokinetics as taught by Namiki with a HGF protein, and to prepare a pharmaceutical composition comprising the PEGylated protein. Even if some pegylation were to decrease activity of the protein, it would have been obvious to experimentally determine which types of pegylation would result in a protein with improved characteristics.

The rejection of claims 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Namiki et al in view of Date et al and Gaertner et al as applied to claims 1-2, 4-6, 8, and 12-13 above, and further in view of and further in view of Veronese et.al. (US Patent 6,528,485 B1), is maintained for the reasons of record in the previous office action mailed on 9/02/2005.

Applicant argues that the Veronese reference is focused on HGRF only and that they do not address PEGlyation of any other protein, such as NK4.
Applicant's arguments have been fully considered but they are not found to be persuassive because the teacings of Date et al in combination with Namiki et al make PEGylation of NK4 obvious as set forth above. Veronese et al. teach making PEGylated proteins and purifying them to greater than 92% purity. Veronese et al teach that with high purity a PEGylated protein would result in a better bioavailability and pharmacokinetics in vivo.
In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

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PRIMARY EXAMINER